Prospective cohort study of breastfeeding and the risk of childhood asthma

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Abbreviations:

aRR – adjusted relative risk, RR – relative risk, WHO – World Health Organization, MoBa – The Norwegian Mother and Child Cohort Study, MBRN – The Medical Birth Registry of Norway, NorPD – The Norwegian Prescription Database, BMI – body mass index, LBW – Low birth weight (<2500g)

Abstract

Background: We aimed to study whether duration of breastfeeding and time for introduction of complementary foods was associated with the risk of childhood asthma, because previous studies show conflicting results.

Methods: We used data from the Norwegian Mother and Child Study, which recruited pregnant women from across Norway between 1999 and 2008. Children with complete data of breastfeeding up to 18 months and current age >7 years were eligible (n=41 020). Asthma as the primary outcome was defined based on ≥2 dispensed asthma medications at age 7 years registered in the Norwegian Prescription Database.

Results: For duration of any breastfeeding, 5.9% of infants breastfed <6 months (adjusted relative risk [aRR] 1.05, 0.93-1.19) and 4.6% breastfed 6-11 months (aRR 0.96, 0.87-1.07) had dispensed asthma medications at 7 years as compared with 4.6% of infants breastfed ≥12 months (P_{trend} 0.62). Infants still breastfed at 6 months, but introduced to complementary foods <4 months and 4-6 months, had an aRR of 1.15 (0.98-1.36) and 1.09 (0.94-1.27) respectively, as compared with infants fully breastfed for 6 months (P_{trend} 0.09). The results of secondary analysis of maternal questionnaire report of asthma at age 7 were similar to the primary analysis, but the risk of asthma at age 3 was increased for the children breastfed <6 months compared with ≥12 months (aRR 1.19, CI 1.07-1.32).

Conclusion: We found no association between duration of breastfeeding or age of introduction to complementary foods and asthma at age 7.

Introduction

The World Health Organization (WHO) recommends to continue full breastfeeding during the first six months of life, a recommendation that has been adopted by several countries. [1] The WHO furthermore recommends partial breastfeeding up to the age of 2, but it is unclear if this is associated with further health, growth and developmental benefits for children in high-income countries. [2, 3]

The prevalence of asthma in children has increased in the second half of the 20th century. [4] Rapid changes in occurrence of disease suggest a potential role for environmental factors, though diagnostic practices may contribute to changing prevalence. Environmental factors in pregnancy and infancy may increase a child's susceptibility to develop asthma. [5]

The role of breastfeeding and the appropriate age for introduction of complementary foods in the prevention of asthma is controversial. Some studies show a reduced risk for asthma in children who are breastfed, while others show no association, or even increased risk. [6-9] Published reviews include a specter of different studies, in addition to cohort studies, also cross-sectional and case control studies. The heterogeneity of previously conducted studies with regard to design, outcome classification and age at outcome classification is likely to influence any pooled measures of association, calling for large cohort studies.

The associations tend to be weaker for asthma defined at an older age compared with early wheezing. [10-15] Asthma before school age likely includes a large proportion of wheezing due to lower respiratory tract infection, while asthma that persists in school age consists of a greater number of children with allergic respiratory symptoms. [16] Based on the current evidence it remains unclear whether the associations differ by asthma phenotypes, defined by age and associated atopic disease.

The aim of this prospective cohort study was therefore to investigate the association of duration of breastfeeding with asthma at age 7 years. We further aimed to study whether the

age for introduction of complementary foods was associated with later asthma. Asthma at age 3 was studied as a secondary outcome.

Material and methods

The Norwegian Mother and Child Cohort Study (MoBa) is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health. [17] Pregnant women were recruited from all over Norway from 1999-2008 at approximately 18 gestational weeks. The participation rate was 41%, and all participants provided a written informed consent. Follow-up was conducted by mailed questionnaires at regular intervals.

The study is based on version VIII of the quality-assured data files released for research on February 14, 2014. In the current study, we use information from six questionnaires; the baseline questionnaire completed around week 18 of pregnancy, questionnaires at child age 6, 18 and 36 months and 7 years and the father's questionnaire (completed at recruitment; questionnaires are available at www.fhi.no/moba). Information gathered through questionnaires was linked to the Medical Birth Registry of Norway (MBRN) and the Norwegian Prescription Database (NorPD) using unique national identification numbers. The current study was approved by the Norwegian Data Inspectorate and the Regional Committee for Medical and Health Research Ethics of South-East Norway.

We included individuals with information from the questionnaire completed at 18 gestational weeks, in addition to questionnaire completed when the child was 6 and 18 months, who had reached 7 years by December 31, 2013 (n=41 020, Figure 1). We decided to use information about asthma medication from the NorPD as the primary outcome to reduce the impact of self-selection at 7 years. Out of the parents who received the 7-year questionnaire, 54% answered and returned it to MoBa. Characteristics of participants with missing exposure information up to age 18 months and thus not included are presented in Table 1.

Outcome: Childhood asthma

The primary outcome was current asthma at 7 years as defined based on dispensed prescriptions in the NorPD. NorPD contains information regarding all dispensed medications in Norway from January 2004 and onwards, and classifies medications according to the Anatomical Therapeutic Chemical classification system. Medications classified as asthma medications were inhaled short- and long-acting beta2-agonists (R03 AC), inhaled corticosteroids (R03 BA), fixed-dose combinations of inhaled beta2-agonists and corticosteroids (R03 AK), and leukotriene antagonists (R03 DC). Children who had at least one dispensed prescription for asthma medications in the past year at the age of 7, in addition to a second dispensed prescription within 12 months of the first, were defined as asthma cases.

As secondary outcomes, we defined current asthma at 3 years and 7 years based on maternal report through questionnaires. Current asthma was defined based on maternal "yes, has now" in response to the question if the child suffered from asthma and reported use of inhaled glucocorticoids and/or beta2-agonists the last 12 months. Positive answers to both asthma diagnosis and use of medications were required for our definition of current asthma.

We classified children with asthma into 3 groups; early transient (asthma at only 3 years), late-onset (asthma onset after 3 years) and persistent asthma (asthma at both 3 and 7 years). These sub-analyses were limited to those who returned questionnaires at both 3 and 7 years.

Exposure: Breastfeeding

In the 6 months' questionnaire, ongoing breastfeeding or formula feeding from the first week in monthly intervals and age at introduction of solids was specified up until completion (median 27 weeks). From 6 to 18 months of age, the mothers reported whether they were breastfeeding in four intervals (6-8, 9-11, 12-14 and 15-18 months). The median value of each interval was used as a fixed value in calculations of breastfeeding duration. For the regression

analyses, we divided duration of any breastfeeding in 3 categories (0-6, 6.1-11.9 and ≥12 months). Breastfeeding was defined as any breastfeeding regardless of whether the child had solids and/or formula.

A second aim was to study the effect of age at introduction of complementary foods (formula or solid foods). Solid complementary foods included porridge, bread or biscuits, fruit purees and processed dinner. To determine this association, we included only children still breastfed at 6 months and divided them into 3 groups based on the age they were introduced to complementary foods, that is, children introduced to complementary foods before 4 months, 4-5.9 months or at 6 months or later. This exposure was defined to study the association with "full breastfeeding", though the current definition allows for water and vitamins, different from the strict definition of exclusive breastfeeding. In analyses of introduction of complementary foods, we also studied separately introduction of formula and solid foods. These sub-analyses were only preformed in the primary group based on dispensed prescriptions in the NorPD.

Covariates

Based on current literature, we chose a number of covariates because they have been associated with asthma in childhood, and additionally may be associated with breastfeeding duration. [18] We extracted information about maternal age, birth weight, gestational age, parity, mode of delivery and gender from the MBRN. The first questionnaire completed around the 18th week of pregnancy held information about maternal education, pre-pregnancy body mass index (BMI) and smoking during pregnancy. The questionnaires at 6 and 18 months answered if the child had been in daycare outside home during the first 18 months of life. We also

considered using pet ownership in the home as a confounder, but the questionnaires gave information limited to before 18 months of age.

Parental asthma and allergy were reported in the father's questionnaire and the mother's questionnaire at recruitment. Parental asthma was defined by the mother and/or father confirming ever having asthma. Parental allergy was defined by the father reporting ever having pollen allergy, and/or the mother reporting ever having pollen allergy or animal hair allergy. Other allergies, e.g. food allergies were not specified in the parental questionnaires, and therefore not included in the parental allergy definition.

The covariates were divided in categories described in Table 2, online, and were used as categorical variables as possible confounders in the analyses.

Statistical analysis

We used log-binomial regression models to obtain crude relative risks (RR) in the main analysis. Multivariable analyses adjusted for the confounders selected *a priori*, and we used the robust variance estimator to account for potential clustering among siblings in the cohort. Similar analyses were conducted in the groups using only questionnaires.

As sub-analyses, we studied age-specific phenotypes of asthma with regression models for children with maternal report of asthma at the age of 3 and/or 7. We performed stratified analyses for children with and without maternal or paternal history of allergy and/or asthma, and we assessed possible interaction between breastfeeding and mode of delivery, sex and maternal BMI.

P values less than 0.05, or a 95% confidence interval not including one, were considered statistically significant. Analyses were performed using Stata 14 (College Station, Texas, US).

Results

Of the 41 020 eligible participants, 79% were still breastfed at 6 months' age and 38% for 12 months or longer. Duration of breastfeeding was positively associated with higher maternal age and education, parity and vaginal delivery. In addition, mothers who continued breastfeeding longer tended to be non-smokers, normal-weight and without history of asthma. The infants who were breastfed longer, started daycare outside home at an older age, and were less likely to be born premature or with low birth weight (LBW). Maternal and infant characteristics by duration of any breastfeeding are described in Table 2, online.

Out of the 41 020 included, 31 930 (78%) were still breastfed at age 6 months. Of those breastfed at age 6 months, 78% had been introduced to solid foods and 36% had supplements with formula before 6 months' age, respectively.

Main analyses – asthma at age 7 based on NorPD

In the main analyses, 4.8% had asthma at 7 years defined by dispensed asthma medications. The absolute risk of asthma was 5.9% among children breastfed up to 6 months, 4.6% from 6 months up to 12 months and 4.6% for 12 months or longer.

The risk of asthma for children with no or any breastfeeding <6 months compared to ≥12 months was increased before adjustments. However, in the adjusted analysis, we observed no significant differences among categories (Figure 2a). Analyzing breastfeeding with a finer categorization yielded similar results (adjusted Relative Risk [aRR] 0.99, 95% CI 0.96-1.02 for every 3 months increased duration, p-value for trend 0.47). Maternal education and pre-pregnant BMI were the strongest confounders.

Analyses of age of introduction to complementary foods (formula and/or solid foods) in children still breastfed at 6 months showed a similar risk with introduction before 6 months

compared with introduction at 6 months or later, and non-significant in adjusted analyses (Figure 2b, p-value for trend 0.09).

When looking at age for introduction of formula separately, the risk of asthma was increased when formula was introduced between 4-5.9 months as compared to 6 months or later (aRR 1.21 [1.03-1.44]), but not for introduction <4 months (aRR 1.10 (0.98-1.25), p-value for trend 0.08, Table 3, online).

The risk of asthma in children introduced to solid foods <4 months was increased before adjustments, however there were no significant differences in the adjusted analyses (p-value for trend 0.16, Table 3, online). Including age for solids and formula foods in the same model yielded similar risk estimates (data not shown).

We tested for interaction between breastfeeding and caesarean section delivery, and found no significant interactions for duration of breastfeeding (p=0.23) nor for age at introduction of complementary foods (p=0.10). We further tested for interaction between breastfeeding and sex, and found no significant interactions (p=0.91 for duration of breastfeeding and 0.58 for age at introduction of complementary foods). Similarly, interaction was not found for breastfeeding and maternal BMI (p=0.94 and 0.93, respectively).

Secondary analyses – asthma at 3 and 7 based on parental report

In the secondary analyses limited to those who had returned questionnaires, the prevalence of asthma based on maternal report was similar to the main analyses, 5.2% at age 3, and 5.4% at age 7 (absolute risk for each breastfeeding category shown in Figure 3).

At the age of 7 questionnaire-based asthma diagnosis was not significantly associated with the duration of breastfeeding after adjustment for confounders. However, at age 3, the risk of asthma was significantly increased for children breastfed less than 6 months compared with 12 months or longer (Figure 3a).

The risk of maternal reported asthma at the age of 3 or 7 was not associated with the age of complementary foods introduction after adjusting for confounders (Figure 3b).

Sub-analysis for asthma phenotypes

For early transient asthma, we found a significantly increased risk for children breastfed less than 6 months compared with 12 months or longer (aRR 1.46 (1.15-1.84), Table 4a, online). We observed no significant associations between duration of breastfeeding with late-onset asthma or persistent asthma. Age of introduction of complementary foods was not significantly associated with asthma in any of the 3 subgroups (Table 4b, online).

Stratified analyses by hereditary predisposition

We subsequently studied the potential influence of hereditary predisposition on the associations. If neither of the parents had allergies or asthma, we found a significantly increased risk of asthma at 7 years based on the NorPD in children with any breastfeeding less than 6 compared with ≥12 months (Table 5, online), (p for interaction between breastfeeding and genetic predisposition = 0.043). We found no association between parental allergy and asthma and age of introduction of complementary foods, and no significant interaction (p=0.21).

We finally studied the potential influence of breastfeeding with stratification of maternal and paternal allergy/asthma separately, as a potential effect has been hypothesized to be mediated through breast milk factors. The associations with breastfeeding duration were similar in the stratum with no maternal compared to no paternal asthma/allergy (Table 5, online).

Discussion

The current nation-wide prospective study suggests that duration of breastfeeding is not associated with asthma at 7 years. Breastfeeding less than 6 months was associated with increased risk of asthma at age 3. Age at introduction of complementary foods in general was not a predictor of asthma neither at age 3 nor 7, though formula before 6 months was a non-consistent risk factor.

Among strengths of the current study is the large sample size from a general population and the prospective data collection, which minimizes potential recall bias. Frequent questionnaires during the child's first years of life reduce the time between exposure and data collection, and increases the accuracy of the data. We were able to adjust for a number of potential confounders, among this detailed parental background information collected before the birth of the child. This reduces the risk of overestimating beneficial effects since breastfeeding is highly influenced by other healthy choices. The high prevalence of breastfeeding in the study limits the power to study the subgroup who did not receive breastmilk, but it provides a good opportunity to study duration of breastfeeding and the introduction of complementary foods.

A potential weakness in our study is the risk of reverse causality.[19] Symptoms of early wheezing or atopic eczema may occur already during breastfeeding, and may impact the mother's motivations for breastfeeding.[20] In the sub-analysis of late-onset asthma, this potential for reverse causality should be minimal. The accuracy of the asthma diagnosis is a further limitation, as we do not have access to individual medical records to verify the diagnosis. However, the strict diagnostic criteria applied for current asthma should reduce the risk of misclassification.

Parental history of atopy may similarly influence the duration of breastfeeding. We thus adjusted for the potential confounding effects of maternal asthma. Adjusting for maternal education and BMI changed the associations substantially. These confounding factors, likely

to be markers of a healthy life style, are important to include in future studies regarding potential effects of breastfeeding. Previous studies differ considerably in the extent of access to such confounders, and this may explain the conflicting results, as recently reviewed.[13]
Both the participation rate into the MoBa cohort and loss to follow-up may have resulted in selection bias.[21] In our study, we observed a greater loss of follow-up in children of mothers with less education and mothers who smoked during pregnancy. Both of these are risk factors for asthma in our study, which may influence the risk estimates in our analyses. To reduce the impact of this self-selection, we decided to define asthma at 7 years by the NorPD, which holds information on all dispensed prescriptions for Norwegian pharmacies since 2004. The prevalence of asthma as defined through NorPD was similar for included (4.8%) and excluded (5.0%). The NorPD asthma definition included inhalation steroids. Use of this medication for other causes (e.g. recurrent pseudocroup, bronchopulmonary dysplasia, eosinophilic esophagitis) may occur, but to a very limited extent.

Comparison with other studies

Our observations are consistent with the findings in the ALSPAC cohort, where lower risk of early wheezing with longer duration of breastfeeding did not extend into later childhood (7.5 years).[22] In the recent study from the Generation R cohort, neither duration nor exclusivity of breastfeeding was associated with asthma at age 10, though some differences in lung function was found.[23] Also in the PROBIT cluster randomized trial, Kramer et al found no indication of reduced risk of asthma at age 6.5 years in a group of children with significantly longer duration and exclusivity of breastfeeding compared with the control group with less breastfeeding.[24]

However, in a review and meta-analysis from 2015, Lodge et al found a reduced risk of asthma associated with more vs. less breastfeeding in ages 5-18 years.[13] This meta-analysis

also includes cross-sectional and case-control studies, which seem to show a greater protective effect than cohort studies, possibly due to recall bias. In line with this assumption, the meta-analysis did not find an association between breastfeeding and asthma when limiting the pooled estimated association to cohort studies. We believe that the present cohort study with its large sample size adds important information.

In our cohort, the prevalence of current asthma at 7 years age was 5%, lower than the 10-11% prevalence reported from other cohorts in Norway,[25, 26] but more similar to the Swedish BAMSE cohort. [27] We have applied a strict definition of asthma as the primary outcome, with asthma medications dispensed twice or more the last 12 months, and the comparable studies have slightly different criteria. Additionally, the mothers consenting to the MoBa study have in general higher socio-economic status and lower rates of smoking. This cohort may thus not be comparable to the general population for prevalence studies. However, the associations between exposure and disease have been shown to be robust to this selection bias.[21]

In the BAMSE cohort, Kull et al found an inverse association of breastfeeding with both early transient asthma and persistent asthma, while there was no association with late-onset asthma.[27] In line with these observations we also found lower prevalence with longer duration of breastfeeding in early transient asthma (3 years). Wheezing before this age is often caused by respiratory virus infections, and some of the previous studies have indicated that breastfeeding may provide protection against viral lower respiratory tract infections.[28-30]

In our study, the age of introduction of complementary foods was not associated with asthma at age 3 or 7. Other studies have also shown that delaying the introduction of common weaning foods beyond 4 or 6 months is unlikely to reduce the likelihood of asthma.[31-33]

In the current study, the association between duration of breastfeeding and asthma differed by genetic predisposition (parental history of asthma). Previous studies have also investigated how maternal asthma or parental allergy influences the association between breastfeeding and

asthma.[34-36] With a longer duration of breastfeeding, Oddy et al found a decreased risk of asthma in children aged 6, regardless of whether the mother had asthma.[35] Scholtens et al found that breastfeeding was associated with a lower risk of asthma in children aged 8, without evidence of effect modification by the family history of allergy.[36] Rothenbacker et al found an inverse association for duration of breastfeeding and the risk for asthma in children aged 2, especially in children of mothers without a history of atopic disease.[34] Similar to our findings, this study may indicate that environmental factors such as early feeding may be of more importance in children with low heredity for asthma. None of these studies are directly comparable due to different categorizations of breastfeeding, age of the children and definitions used for asthma.

Conclusion

In this large, prospective birth cohort we found no association between asthma at age 7 and duration of any breastfeeding. Early introduction of complementary foods did not influence the association. Sub-analyses indicated that breastfeeding was associated with reduced risk in children with a low family risk of asthma.

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Table and Figure Legends

Table 1: Characteristics of included and non-included participants.

Figure 1: Flow chart of participants in the study.

Figure 2: Association Between Asthma and Breastfeeding at Age 7 based on NorPD

aRR = Adjusted Relative Risk, RR = Relative Risk
The analyses were adjusted for infant gender, birth weight, gestational age, parity, caesarean section and start of daycare outside home and maternal age, smoking, BMI, education and asthma. For age of introduction of complementary foods, only infants still receiving breastmilk at age 6 months were analyzed.

Figure 3: Secondary analyses – asthma at 3 and 7 based on maternal report

aRR = Adjusted Relative Risk, RR = Relative Risk
The analyses were adjusted for infant gender, birth weight, gestational age, parity, caesarean section and start of daycare outside home and maternal age, smoking, BMI, education and asthma. For age of introduction of complementary foods, only infants still receiving breastmilk at age 6 months were analyzed.

Table 1

Table 1: Characteristics of included and non-included participants.

Mother	***Included NorPD % (n=41 020)***	***Not included % (n=31 402)***
Age, % (n)		
<25 years	10.3% (4235)	8.1% (2547)
25-34 years	73.2% (30 042)	72.4% (22 731)
≥35 years	16.4% (6743)	19.5% (6124)
Education, % (n)		
Less than high school	2.1% (858)	1.8% (552)
High school	33.4% (13 708)	22.5% (7053)
Up to 4 years of university	43.0% (17 637)	43.0% (13 504)
More than 4 years of university	21.5% (8817)	32.8% (10 293)
Caesarean section, % (n)		
Yes	14.2% (5808)	14.9% (4670)
History of asthma, % (n)		
Yes	7.0% (2883)	7.6% (2370)
History of allergy, % (n)		
Yes	21.7% (8892)	24.0% (7524)
Smoking during pregnancy *, % (n)		
No	90.4% (37 087)	95.0% (29 821)
Occasionally	3.0% (1238)	1.6% (513)
Daily	5.9% (2423)	2.7% (861)
Parity, % (n)		
0	45.1% (18 485)	50.8% (15 936)
1	34.6% (14 205)	33.6% (10 563)
2+	20.3% (8330)	15.6% (4903)
BMI †, % (n)		
<25	66.4% (27 249)	69.1% (21 703)
25-30	21.6% (8853)	20.5% (6430)
≥30	9.2% (3769)	8.4% (2632)
Father		
History of asthma ‡, % (n)		
Yes	6.0% (2442)	7.8% (2434)
History of allergy ‡, % (n)		
Yes	13.2% (5419)	16.6% (5218)
Child		
Male gender	51.0% (20 904)	51.3% (16 123)
Birth weight §, % (n)		
<2500g	4.0% (1631)	3.7% (1149)
2500-3499g	36.6% (14 996)	39.9% (12 531)
3500-4499g	54.6% (22 377)	52.6% (16 527)
≥4500g	4.9% (1991)	3.7% (1176)
Gestational age ‖, % (n)		
<37 weeks	6.1% (2491)	5.5% (1725)
≥ 37 weeks	93.5% (38 370)	94.0% (29 527)
Start of daycare outside home, % (n)		
Before 6 months	0.2% (64)	0.3% (108)
Between 6 and 12 months	14.6% (4573)	12.8% (5235)
Between 12 and 18 months	65.9% (20 684)	50.4% (20 689)
No daycare outside home	19.4% (6081)	36.5% (14 988)
Duration of full breastfeeding, % (n)		
<4 months	39.5% (16 191)	41.2% (12 941)
4-5.9 months	45.9% (18 811)	44.5% (13 989)
≥6 months	14.7% (6018)	14.2% (4472)
Duration of any breastfeeding, % (n)		
0-6 months	20.7% (8477)	19.0% (5981)
6.1-11.9 months	41.7% (17 109)	41.4% (12 997)
≥12 months	37.6% (15 434)	39.6% (12 424)

NorPD – The Norwegian Prescription Database, BMI – Body mass index
* missing 479 † missing 1786 ‡ missing 17269 § missing 44 ‖ missing 309

Figure 1

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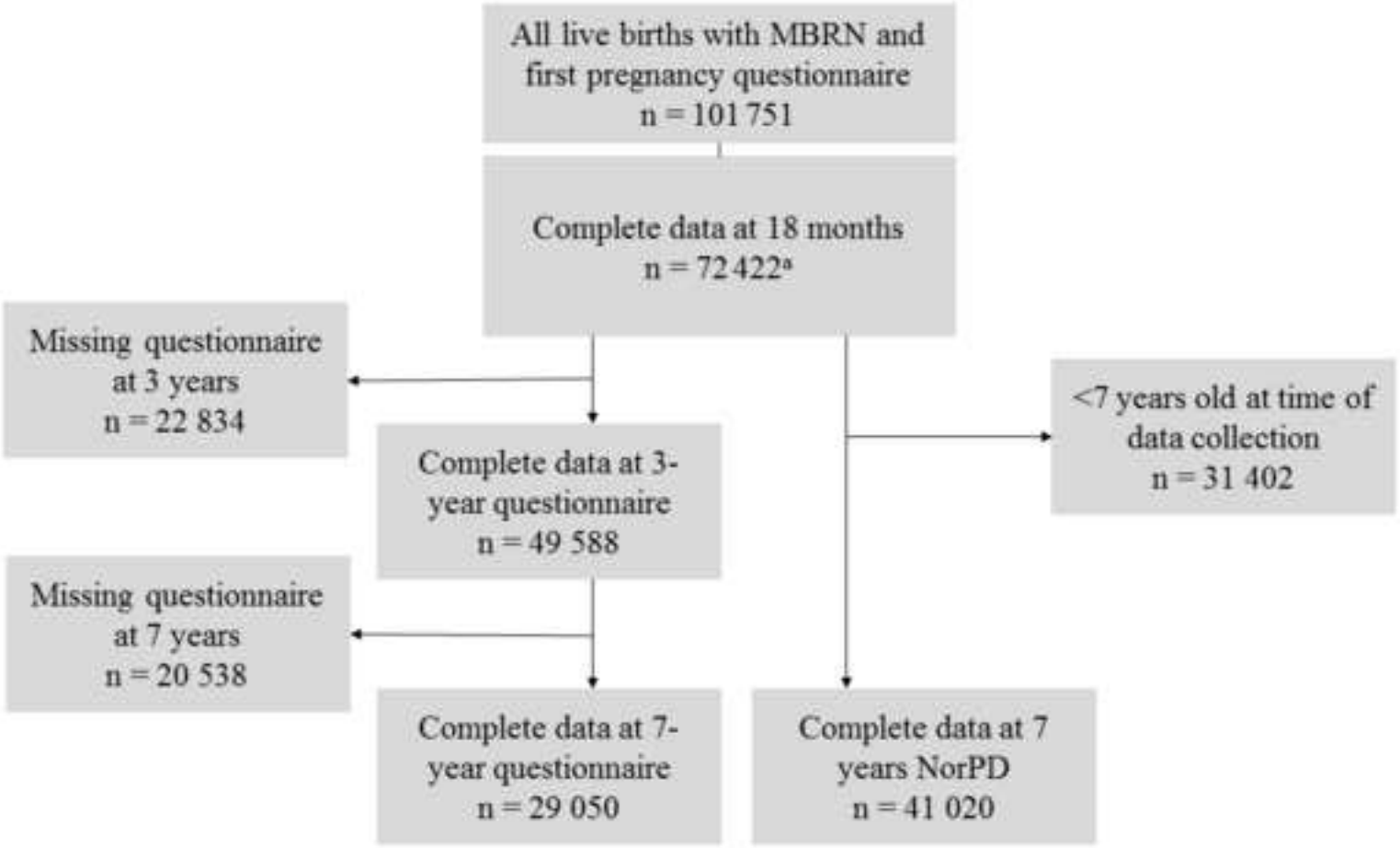

MBRN – The Medical Birth Registry of Norway, NorPD – The Norwegian Prescription Database

[a]Missing 6-month and/or 18-month questionnaire (n=28329)

Figure 2

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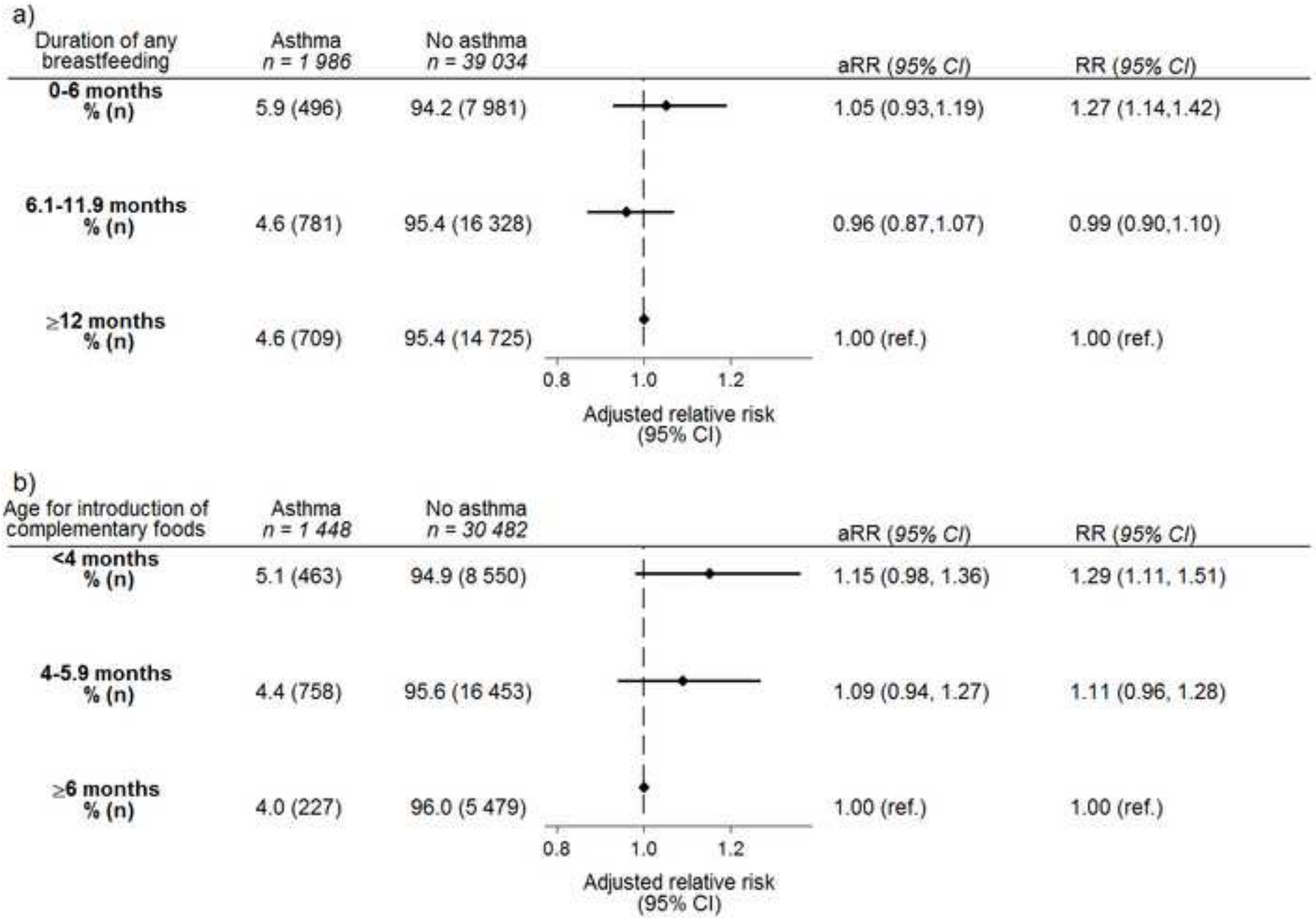

Figure 3

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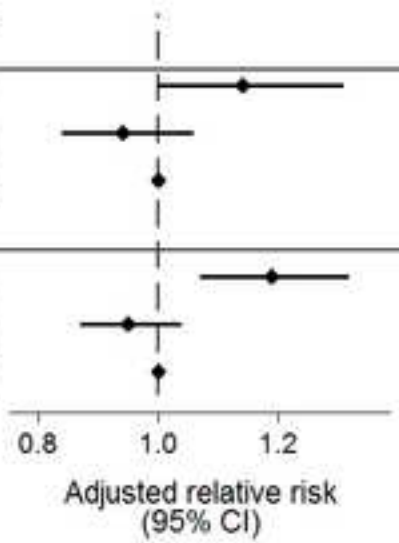
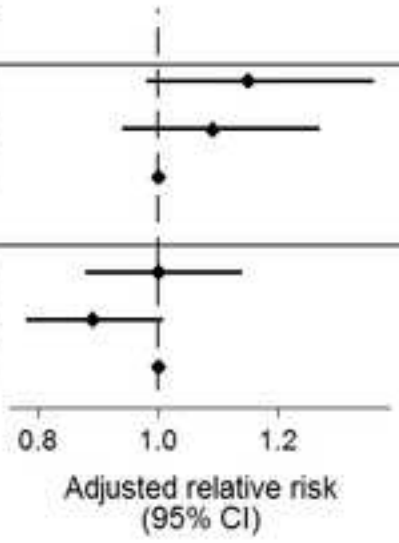
a)

Duration of any breastfeeding	Asthma *7 yrs*	No asthma *7 yrs*	aRR (*95% CI*)	RR (*95% CI*)
0-6 months, % (n)	7.1 (387)	92.9 (5 081)	1.14 (1.00,1.31)	1.39 (1.23,1.58)
6.1-11 months, % (n)	5.0 (609)	95.0 (11 632)	0.94 (0.84, 1.06)	0.98 (0.88,1.09)
≥12 months, % (n)	5.1 (577)	94.9 (10 764)	1.00 (ref.)	1.00 (ref.)
	3 yrs	*3 yrs*		
0-6 months, % (n)	6.7 (624)	93.4 (8 761)	1.19 (1.07, 1.32)	1.36 (1.23, 1.50)
6.1-11 months, % (n)	4.9 (1005)	95.1 (19 661)	0.95 (0.87, 1.04)	0.99 (0.91, 1.08)
≥12 months, % (n)	4.9 (956)	95.1 (18 581)	1.00 (ref.)	1.00 (ref.)



b)

Age for introduction complementary foods	Asthma *7 yrs*	No asthma *7 yrs*	aRR (*95% CI*)	RR (*95% CI*)
<4 months, % (n)	5.8 (381)	94.3 (6 242)	1.08 (0.91, 1.28)	1.20 (1.02, 1.42)
4-5.9 months, % (n)	4.7 (591)	95.3 (11 883)	0.96 (0.82, 1.13)	0.99 (0.85, 1.16)
≥6 months, % (n)	4.8 (198)	95.2 (3 938)	1.00 (ref.)	1.00 (ref.)
	3 yrs	*3 yrs*		
<4 months, % (n)	5.5 (640)	94.5 (10 985)	1.00 (0.88, 1.14)	1.09 (0.96, 1.24)
4-5.9 months, % (n)	4.6 (960)	95.5 (20 137)	0.89 (0.78, 1.01)	0.90 (0.80, 1.02)
≥6 months, % (n)	5.0 (351)	95.0 (6 621)	1.00 (ref.)	1.00 (ref.)



Appendix

Table 2, online only: Maternal and infant characteristics by duration of any breastfeeding.

Duration of Any Breastfeeding n=41 020	**0-6 Months** n=8477	**6.1-11.9 Months** n=17109	**≥12 Months** n=15 434	**p-value***
Maternal age, % (n)				
<25	17.5% (1482)	10.7% (1831)	6.0% (922)	<0.001
25-34	68.7% (5823)	75.5% (12 910)	73.3% (11 309)	
≥35	13.8% (1172)	13.8% (2368)	20.8% (3203)	
Maternal education, % (n)				
Less than high school	2.5% (210)	2.0% (348)	1.9% (300)	<0.001
High school	51.6% (4378)	32.8% (5615)	24.1% (3715)	
Up to 4 years of university	34.8% (2950)	44.5% (7616)	45.8% (7071)	
More than 4 years of university	11.1% (939)	20.6% (3530)	28.2% (4348)	
Maternal smoking[†]*, % (n)*				
No	81.9% (6939)	91.3% (15 627)	94.1% (14 521)	<0.001
Occasionally	4.8% (410)	3.1% (526)	2.0% (302)	
Daily	12.6% (1069)	4.9% (840)	3.3% (514)	
Caesarean section, % (n)				
Yes	20.3% (1721)	12.8% (2197)	12.2% (1890)	<0.001
Maternal history of asthma, % (n)				
Yes	8.6% (731)	6.4% (1097)	6.8% (1055)	
Parity, % (n)				
0	51.1% (4333)	44.7% (7648)	42.1% (6504)	<0.001
1	33.3% (2820)	36.2% (6192)	33.6% (5193)	
2+	15.6% (1324)	19.1% (3269)	24.2% (3737)	
BMI[‡]*, % (n)*				
<25	56.5% (4788)	67.8% (11 597)	70.4% (10 864)	<0.001
25-29.9	24.7% (2090)	21.5% (3673)	20.0% (3090)	
≥30	15.6% (1326)	8.0% (1368)	7.0% (1075)	
Start of daycare outside home				
Before 6 months	0.5% (46)	0.2% (41)	0.1% (21)	<0.001
6-12 months	14.1% (1196)	14.3% (2440)	10.4% (1599)	
12-18 months	45.2% (3834)	51.8% (8855)	51.8% (8000)	
No daycare before 18 months	40.1% (3401)	33.7% (5773)	37.7% (5814)	
Gestational age[§]*, % (n)*				
<37 weeks	10.3% (874)	5.2% (891)	4.7% (726)	<0.001
≥37 weeks	89.3% (7571)	94.4% (16 155)	94.9% (14 644)	
Birth weight[‖]*, % (n)*				
<2500 g	7.6% (642)	3.2% (545)	2.9% (444)	<0.001
2500-3499g	39.1% (3315)	35.9% (6138)	35.9% (5543)	
3500-4499g	48.4% (4106)	56.1% (9590)	56.2% (8681)	
≥4500g	4.8% (407)	4.8% (828)	4.9% (756)	
Gender, % (n)				
Male	52.0% (4406)	52.5% (8977)	48.7% (7521)	<0.001

[*] Chi-square test, [†] missing 272, [‡] missing 1149, [§] missing 159, [‖] missing 25

Table 3, online only: Risk of asthma at age 7 as defined by dispensed prescriptions by age of introduction of formula and solid foods in children still breastfed at age 6 months (n=31 930).

	Months	Asthma (%)	No asthma (%)	Crude RR (95% CI)	Adjusted RR* (95% CI)
Age at formula introduction	<4	426 (5.1)	7925 (94.9)	1.21 (1.08-1.36)	1.10 (0.98-1.25)
	4-5.9	168 (5.2)	3093 (94.9)	1.23 (1.04-1.44)	1.21 (1.03-1.44)
	>=6	854 (4.2)	19464 (95.8)	1 (ref.)	1 (ref.)
Age at solids introduction	<4	72 (6.1)	1119 (94.0)	1.41 (1.10-1.81)	1.28 (0.98-1.66)
	4-5.9	1072 (4.5)	22578 (95.5)	1.06 (0.93-1.20)	1.05 (0.92-1.20)
	>=6	304 (4.3)	6785 (95.7)	1 (ref.)	1 (ref.)

* The analyses were adjusted for infant gender, birth weight, gestational age, parity, caesarean section, duration of any breastfeeding, start of daycare outside home, maternal age, smoking, BMI, education and asthma.

Table 4, online only: Association between asthma phenotypes and a) duration of any breastfeeding and b) introduction of complementary foods.

a)

	N	Duration breastfeeding in months	Asthma (%)	No asthma (%)	Crude RR (95% CI)	Adjusted RR (95% CI)
Early Transient Asthma	22 918	≥12	188 (2.1)	8890 (97.9)	1	1
(Asthma only at age 3)		6.1-11.9	220 (2.3)	9455 (97.7)	1.10 (0.91-1.34)	1.00 (0.82-1.22)
		0-6	137 (3.3)	4028 (96.7)	1.60 (1.28-1.98)	1.46 (1.15-1.84)
Late Onset Asthma	22 929	≥12	208 (2.3)	8890 (97.7)	1	1
(Asthma only at age 7)		6.1-11.9	217 (2.2)	9455 (97.8)	0.98 (0.81-1.19)	0.94 (0.78-1.15)
		0-6	131 (3.1)	4028 (96.9)	1.38 (1.12-1.72)	1.12 (0.89-1.41)
Persistent Asthma	22 857	≥12	213 (2.3)	8890 (97.7)	1	1
(Asthma at age 3 and 7)		6.1-11.9	214 (2.2)	9455(97.8)	0.95 (0.78-1.14)	0.91 (0.75-1.11)
		0-6	130 (3.1)	4028 (96.9)	1.35 (1.09-1.67)	1.15 (0.91-1.45)

* The analyses were adjusted for infant gender, birth weight, gestational age, parity, caesarean section, start of daycare outside home, maternal age, smoking, BMI, education and asthma.

b)

	N	Age complementary foods in months*	Asthma (%)	No asthma (%)	Crude RR (95% CI)	Adjusted RR† (95% CI)
Early Transient Asthma	18 512	≥6	67 (2.0)	3209 (98.0)	1	1
(Asthma only at age 3)		4-5.9	202 (2.0)	9843 (98.0)	0.98 (0.75-1.29)	0.89 (0.67-1.18)
		<4	131 (2.5)	5060 (97.5)	1.24 (0.92-1.65)	1.08 (0.80-1.47)
Late Onset Asthma	18 529	≥6	61 (1.9)	3209 (98.1)	1	1
(Asthma only at age 7)		4-5.9	215 (2.1)	9843 (97.9)	1.16 (0.88-1.55)	1.10 (0.82-1.47)
		<4	141 (2.7)	5060 (97.3)	1.47 (1.09-1.98)	1.34 (0.98-1.84)
Persistent Asthma	18 538	≥6	75 (2.3)	3209 (97.7)	1	1
(Asthma at age 3 and 7)		4-5.9	214 (2.1)	9843 (97.9)	0.95 (0.73-1.23)	0.92 (0.70-1.21)
		<4	137 (2.6)	5060 (97.4)	1.19 (0.90-1.57)	1.04 (0.77-1.40)

* The analyses only include children still breastfed at 6 months.

† The analyses were adjusted for infant gender, birth weight, gestational age, parity, caesarean section, duration of any breastfeeding, start of daycare outside home, maternal age, smoking, BMI, education and asthma.

Table 5, online only: Association between duration of any breastfeeding and asthma at age 7 stratified by parental, maternal and paternal asthma and allergy.

	N	Asthma (%)	No asthma (%)	Duration breastfeeding	Crude RR (CI 95%)	Adjusted RR* (CI 95%)
Parental allergy or asthma	12 160	295 (6.3)	4371 (93.7)	≥12 months	1	1
		307 (6.2)	4645 (93.8)	6.1-11.9 months	0.98 (0.84-1.14)	0.93 (0.79-1.09)
		195 (7.7)	2347 (92.3)	0-6 months	1.21 (1.02-1.44)	0.97 (0.80-1.17)
No parental allergy or asthma	16 629	170 (2.8)	5908 (97.2)	≥12 months	1	1
		236 (3.3)	6851 (96.7)	6.1-11.9 months	1.19 (0.98-1.45)	1.09 (0.89-1.34)
		154 (4.5)	3310 (95.6)	0-6 months	1.59 (1.28-1.97)	1.33 (1.05-1.68)
Maternal allergy or asthma	10 061	288 (7.4)	3614 (92.6)	≥12 months	1	1
		285 (7.1)	3759 (93.0)	6.1-11.9 months	0.95 (0.82-1.12)	0.94 (0.80-1.11)
		181 (8.6)	1934 (91.4)	0-6 months	1.16 (0.97-1.39)	0.92 (0.76-1.12)
No maternal allergy or asthma	30 959	421 (3.7)	11111 (96.4)	≥12 months	1	1
		496 (3.8)	12569 (96.2)	6.1-11.9 months	1.04 (0.92-1.18)	0.97 (0.85-1.11)
		315 (5.0)	6047 (95.1)	0-6 months	1.36 (1.18-1.56)	1.15 (0.99-1.35)
Paternal allergy or asthma	6 825	171 (6.5)	2475 (93.5)	≥12 months	1	1
		173 (6.2)	2612 (93.8)	6.1-11.9 months	0.96 (0.78-1.18)	0.92 (0.74-1.13)
		107 (7.7)	1287 (92.3)	0-6 months	1.19 (0.94-1.50)	0.98 (0.76-1.26)
No paternal allergy or asthma	21 964	294 (3.6)	7804 (96.4)	≥12 months	1	1
		370 (4.0)	8884 (96.0)	6.1-11.9 months	1.10 (0.95-1.28)	1.01 (0.87-1.18)
		242 (5.3)	4370 (94.8)	0-6 months	1.46 (1.22-1.71)	1.16 (0.96-1.39)

* The analyses were adjusted for infant gender, birthweight, gestational age, parity, caesarean section and start of daycare outside home and maternal age, smoking, BMI and education.